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COMMENTARY

The Economic Conundrum for Antibacterial Drugs

David M. Shlaes[a]

[a]Anti-Infectives Consulting (retired), Stonington, Connecticut, USA

ABSTRACT While resistance to antibacterial drugs is increasing globally, it is unevenly distributed. The number of cases that are truly difficult to treat remain below the number required to drive an adequate market for needed new therapies. Without a sufficient market, companies pursuing these drugs risk financial failure. Here, I explore, at least briefly, the current situation and the financial risks to companies. I provide potential solutions to the failed market.

KEYWORDS antibacterial drugs, antibacterial research, antimicrobial resistance, commercial markets, drug development

The most recent data from the U.S. Centers for Disease Control and Prevention (CDC) shows that during the years 2011 to 2014, 20% of *Klebsiella* spp. from invasive infections are resistant to third-generation cephalosporins, and 3.5% of *Enterobacteriaceae* are resistant to carbapenem antibiotics (1). European data show that *Klebsiella* spp. from some countries have rates of third-generation cephalosporin resistance of >50% and, while carbapenem-resistant *Klebsiella* spp. are less common, Italy and Greece have frequencies ranging from 25% to more than 50% (2). It is also clear that infections with resistant pathogens are associated with higher mortality rates. Although this association is multifactorial, delayed appropriate therapy is an important contributor to this increased likelihood of death from these infections (3–6).

While these numbers are frightening, a recent large national study from the United States examined the frequency of "difficult to treat" infections defined as those caused by Gram-negative pathogens resistant to all B-lactam antibiotics, including carbapenems and fluoroquinolones. This study reported that among bacteremic infections, only 1% fell into this category (7). Resistance is epidemiologically "spotty." Although some centers, and indeed some countries, might be experiencing high frequencies of highly resistant infections, others have been virtually completely spared. This explains, in part, the market challenge for new antibacterial drugs.

Most experts agree that a viable antibacterial drug pipeline is needed to be able to deal with emerging resistance to both old and new drugs (8). As shown in Fig. 1, the antibacterial drug market is large at $42 billion, but it is not nearly as large as markets for oncology, inflammation, and diabetes (9; Mike Pucci, Spero Therapeutics, unpublished data). Of a total pharmaceutical market of $1.2 trillion, the antibacterial market seems small indeed. This market is also, unlike other drug markets, highly genericized, with many antibacterials available at pennies per day of therapy. We must remember that antibacterial drugs were among the first to be developed and marketed by the industry with the sulfonamides in the 1930s and penicillin in 1945.

The antibacterial market is challenged by a number of major factors: (i) the market is highly genericized; (ii) small numbers of patients require newer therapies; (iii) antimicrobial stewardship enforces appropriate use; (iv) the significant lag time between drug approval and clinical guidelines for its use; and (v) the significant delay in the availability of automated susceptibility testing capability. The need to restrict the use of new (and old) agents to circumstances where their use is clearly indicated is important to preserve the utility of these precious commodities (10). The levels of

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Address correspondence to Shlaes.david@earthlink.net.

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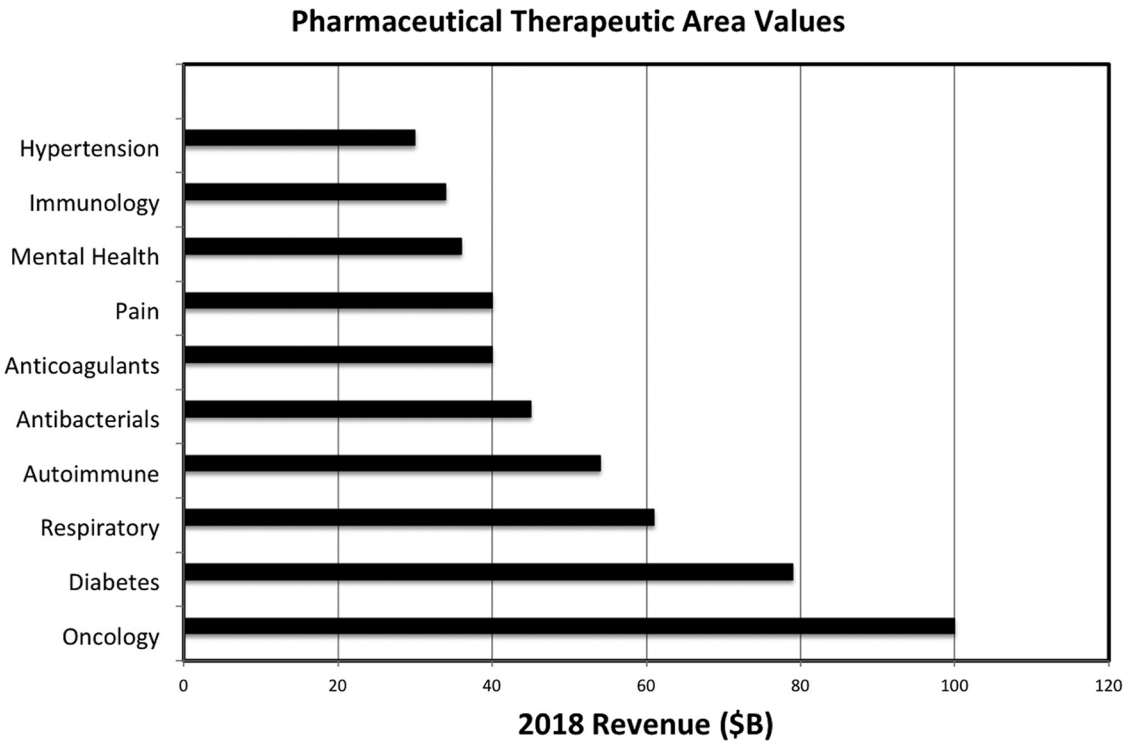

FIG 1 Pharmaceutical market, 2018.

resistance globally are not high enough to establish a robust market for new antibacterials active against these resistant strains (11, 12). The fact that clinical guidelines are woefully behind the introduction of new and useful antibacterials to the marketplace delays their uptake by physicians, pharmacists, and hospital formularies (13). Finally, the delay from the market introduction of a new antibacterial drug to the availability of automated susceptibility testing capability for hospitals further impedes the uptake of new agents (14).

The paltry revenues engendered by recent launches of recently approved antibacterials illustrate the effect of these variables on the market (Table 1). Investors are also paying attention. The market capitalization data for a number of publicly held biotech companies marketing or developing new antibacterial drugs are listed in Table 2. Once this level of support drops below $100 million, it is difficult for a company to maintain a cash flow sufficient to meet their costs (see below). This is especially important during the first years after the introduction of a new agent.

Once a new agent is approved, the sponsoring company acquires a number of obligations. They may want to carry out additional phase 3 trials to obtain additional indications. These trials can cost from $25 million to well over $100 million, depending on the indication sought. The sponsor may need to carry out additional pharmacovigilance activities, and they will certainly need to survey for microbial resistance by

TABLE 1 Recent U.S. sales of new antibacterial drugs[a]

Drug	Company	Approval date (yr)	Sales, last 12 mo ($ [US], in millions)
Vabomere	Melinta	2017	11
Minocycline	Melinta	2015	11
Delafloxacin	Melinta	2017	11
Plazomicin	Cipla	2018	1
Ceftazidime-avibactam	Allergan	2015	102
Ceftolozane-tazobactam	Merck	2014	53

[a]These IQVIA data from Alan Carr cover a 12-month period (August 2018 through July 2019).

TABLE 2 Market capitalization, October 2019[a]

Company	Market cap ($ [US], in millions)
Entasis	75
Iterum	60
Melinta	48
Nabriva	128
Paratek	114
Spero	191
Tetraphase	206

[a]Data from Yahoo Finance. Tetraphase recently consolidated its stock with a 20-to-1 reverse split to increase its market capitalization.

carrying out virtually constant surveillance. All this requires additional investment. In addition, the sponsor must partner with experts and thought leaders in an effort to inform clinicians, pharmacists, and others on the appropriate use of the drug. Information on potential side effects, toxicities, and other safety issues also requires dissemination at the time of launch. All this must be accomplished in a way that is consistent with the labeling the sponsor has negotiated with the regulatory agencies. The costs of all of these efforts fall mostly on the sponsor. Not counting the costs of additional phase 3 trials, estimates of postapproval budgets that I have received from marketing executives and chief executive officers of publicly held biotech companies range from a low of $8 million to $30 million and more for the first year postapproval.

For new agents that address uncommon diseases that nevertheless pose a significant burden on the health care system, sponsors sometimes have to spend resources prior to approval showing how the putative new agent can ameliorate the situation. A good example of this is the first conjugate pneumococcal vaccine developed by Wyeth, Prevnar. Several years prior to approval, the medical need for such a vaccine for children was not widely appreciated since individual clinicians saw invasive pneumococcal infections only occasionally. With a new vaccine for children in the pipeline, the Infectious Diseases Society of America, the CDC, Wyeth Pharmaceuticals, and other stakeholders carried out a number of studies on the burden of invasive pneumococcal infection both in the United States and around the world (15). This was an important step from the public health point of view, and it occurred preapproval. These data were instrumental in providing a rationale for the immediate recommendation of the vaccine for the birth cohort.

It is not at all clear to me that the costs of these important pre- and postmarket activities would disappear under a scenario where revenue was delinked from sales volume, as many have suggested (16).

Given the market conditions for new antibacterial therapeutics, most large pharmaceutical companies abandoned the area long ago. This trend has continued in recent years with the loss of Novartis, Astra-Zeneca, and Sanofi (17). Today, 80 to 90% of new antibacterial drugs either recently approved or in the development pipeline are owned by small companies (18). The Pew Charitable Trust and other experts have shown that in spite of the number of small companies actively pursuing antibacterial research and development today, the pipeline for new agents remains inadequate to ensure a future with products active against resistant pathogens (8, 18). These companies and the few large companies still pursuing antibacterial drug research and development have been helped considerably by the availability of public funds to support their activities. A consortium of funders, including the Wellcome Trust, the Biomedical Advanced Research and Development Authority (BARDA), the National Institutes of Health (who provides in-kind assistance), and others, has coalesced in CARB-X. CARB-X funds the research phase of development through early phase I trials in humans. BARDA, separately, funds the clinical development of new antibacterials that answer prioritized medical needs from phase II development to approval. For certain products, BARDA can even provide for an early upfront purchase of a designated amount of product for the national stockpile in case of a bioterror attack. However, this funding is only partial.

When CARB-X was first established, companies were expected to provide at least 30% of the costs of research and development themselves (K. Outterson, unpublished data). Today, the cost share is 10 to 20% (19). The companies must be able to demonstrate that they are and will continue to be commercially viable through the term of the grants they receive. CARB-X and BARDA provide these monies under a contract arrangement with milestones, and funding can be discontinued if milestones are not met or if the company suffers a financial setback that precludes their ability to continue work on the contracted project.

The awards by BARDA through CARB-X and its Antibacterials Program are extremely important for all developers pursuing the research and development of critically needed antibacterials. Importantly, the funding provided does not dilute investment provided by others and also provides a critical external validation of the projects. As of July 2019, CARB-X has committed $109 million to support the early-stage development of promising antibacterial therapeutic candidates (Outersson, unpublished). BARDA's antibacterials program has invested more than $1.1 billion in the fight against antimicrobial resistance, including $1.01 billion ($58.6 million for CARB-X) specifically on therapeutic antibacterial candidates (R. Bright, unpublished data).

BARDA and others have recognized that these investments are important but also that additional support is needed to assist developers with the cost of commercialization for their newly approved products. Earlier this year, BARDA announced they were "exploring" strategies in this space, including commercial market strengthening initiatives.

Unfortunately, none of this help will save a company from commercial failure. The recent failure of Achaogen, according to some, illustrates what happens when a company overspends on research and the development of a product with a very limited market potential. However, their experience also highlights how the conditions following approval are unsustainable for a company that does not have other revenues it can sacrifice to subsidize the antibiotic's losses. For Achaogen and other non-revenue-generating biotech companies, the only sources of capital are funds raised either through the issuance of stock or debt. The collapse of investor sentiment in the antibiotic sector has resulted in a series of small companies becoming "trapped" with cash in hand to operate for another 6 to 12 months, but no mathematically viable way to finance to sustainability. An estimate of the costs to reach the break-even line approach $250 to $400 million for an individual product. Most of these costs are per product, meaning that having more than one product amplifies the need for capital (R. Cirz, unpublished data). To raise this amount of capital for a single product requires a company to carry market capitalization of $1 to $2 billion. NASDAQ requires shareholder approval to raise funds beyond 20% of its market capitalization (20). The seven publicly traded antibiotic companies listed in Table 2 have a mean market capitalization of $117 million. The maximum the average company can readily raise is therefore $23 million, less than one-tenth the capital required to reach sustainability.

Two recent attempts at dealing with the broken antibiotics market target reimbursement of expensive new antibacterials. In the United Kingdom, the National Institute for Health Care Excellence (NICE) is planning to provide value-based reimbursement for antibiotics active against resistant infections (21). Since NICE has only recently invited already-approved drugs to apply for this incentive, we cannot judge how effective it is likely to be. In the United States, the Centers for Medicare and Medicaid Services (CMS) announced that they will expand their existing New Technology Add-On Payment to new antibiotics meeting critical medical needs, such that 75% of their cost can be added to the normal Diagnostic Related Group payment instead of the previous 50% limit. The CMS also will allow resistant infections to be classified as complicated care under their reimbursement scheme. This should also increase payments to hospitals for patients with resistant infections (22). The rationale for these steps would be to increase the uptake of new, expensive antibiotics by hospitals and therefore increase the revenues generated. Although these plans may be a step forward, it seems unclear whether they will be sufficient to provide a return on

investment in antibacterial research and development and therefore an incentive for investors or large pharmaceutical companies.

The DISARM bill, now before Congress (23), would provide 100% reimbursement for new and needed antibacterial drugs. This reimbursement may come without the bureaucratic requirements of NTAP and, as such, may be more acceptable to hospitals. What DISARM may not accomplish is to provide enough of a return on investment in these new antibacterial drugs without an increase in use caused by increased resistance (12), something none of us wants to see. We may need to support the market in the absence of enough resistant infections to sustain such a market without such support.

Another solution would be to establish a public-private institute, or even a fully publicly funded research and development effort, to provide the pipeline of antibiotics we will need to ensure a safe future (8, 24). In that way, we could avoid providing funding to a pharmaceutical industry that many find abhorrent. Once again, though, the challenges to finding the level of funding this would require, either from public or private sources, in the absence of a larger pubic health crisis seem great.

If we, as a global society, are unable to address the failure of the free market to provide a return on investment in new antibiotics that we know will be required to provide physicians and patients the ability to treat resistant infections, we will ultimately suffer the consequences. The Antimicrobial Review has estimated that if current trends continue, we will see 10 million excess deaths and a loss of $100 trillion to the global gross domestic product by the year 2050 (8). To address these concerns, we should consider a number of concrete steps, none of which are mutually exclusive.

In any attempt to address the broken market, we must provide for a return on investment in antibacterial research and development. This will provide an incentive for investors to return to the space. Without investors and their capital, it will be difficult, if not impossible, to maintain our pipeline of new antibacterial drugs for the resistant infections of the future. Another target for incentives is large pharmaceutical companies. If they reenter the space, this in turn will provide a strong motivating factor for investors who believe that the deep pockets of these companies are the most likely source for a return on their investment.

In order to secure a viable future in the face of rising antibiotic resistance, I believe that leveraging the existing pharmaceutical industry, both small and large, will be required. To accomplish this, a very significant pull incentive is necessary to provide a return on investment for companies that discover and develop needed new antibiotics. That said, a recent report from the Chatham House laments the lack of progress in providing market incentives for investment in antibiotic research and development (25).

I recommend a number of actions. (i) It would be helpful to provide a direct government-funded reward for the approval of antibacterial therapies meeting predefined high priority medical needs. This could be accomplished via a so-called market entry reward (16) of around $1 to $2 billion paid out over 4 to 5 years on a contractual basis that obligates the recipient company to carry out a number of tasks related to manufacturing, distribution, education, and provision for good stewardship of their new product. The price they could then charge would be restricted either permanently or for a defined period of time. (ii) Another approach would be to provide a transferable exclusivity voucher. This would allow a company to have an extension on exclusive sales of an already marketed product of their choice upon receiving approval to market a high priority antibacterial drug. This voucher would have to come with "guardrails" to limit the benefit received to the same $1 to $2 billion noted above and would be part of a similar contractual arrangement. (iii) Others (8) have also suggested a "play or pay" approach to the problem. This would provide a reward for having an active antibiotic research and development program but impose a payment requirement for those companies not pursuing antibiotics research. However, I have not seen a practical workable proposal for the implementation of such a plan.

I understand the extreme hesitancy to reward pharmaceutical companies with additional funds, even though this might be required to save the antibacterial

market. Other steps we could take are noted below. (i) In parallel with market support for new, high-priority antibacterial drugs today, we should consider investing in a publicly funded research and development organization to take over this task from private industry. Since I believe such a plan would take 15 to 20 years to bring needed new products to market, funding such an organization now would provide a buffer of time while the publicly funded organization comes up to speed. (ii) Expert societies such as the Infectious Diseases Society of America, the American Thoracic Society, and their sister organizations around the globe need to provide either real-time or at least annual guidelines on the use of antibacterial agents, including new products recently introduced to the market. This guidance has demonstrably affected sales of drugs (13). Such a move would increase the rapidity of uptake of new drugs in spite of the high prices that may be charged for treatment. Moreover, it would help alleviate our current market malaise. (iii) We need a requirement for manufacturers of automated susceptibility testing devices to offer the ability to test for new antibacterials within one year of approval. It is hard for physicians to prescribe treatments without these key data (14).

In conclusion, in spite of rising antimicrobial resistance on a global scale, the level of resistance has not yet achieved a level that can sustain a market for new antimicrobials effective in the treatment of these resistant infections. If we wait for a global pandemic, in the absence of a viable pipeline of new antibiotics, we will be forced to wait for the resulting newly motivated antibiotic research and development to respond effectively. This will require 10 to 15 years. To avoid such a devastating scenario, we need to invest now.

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